Osteoarthritis and Cartilage 18 (2010) 1275–1283

Osteoarthritis and Cartilage

Reference values and Z-scores for subregional femorotibial cartilage thickness – results from a large population-based sample (Framingham) and comparison with the non-exposed Osteoarthritis Initiative reference cohort

F. Eckstein †*, M. Yang ‡, A. Guermazi §, F.W. Roemer §, M. Hudelmaier †, K. Picha ||, F. Baribaud ||, W. Wirth †, D.T. Felson ‡

† *Paracelsus Medical University & Chondrometrics GmbH, Salzburg, Austria*
‡ *Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, MA, USA*
§ *Department of Radiology, Boston University School of Medicine, Boston, MA, USA*
|| *Centocor Inc., Radnor, PA, USA*

ARTICLE INFO

Article history:
Received 14 December 2009
Accepted 27 July 2010

Keywords:
Normal values
Cartilage thickness
Z-scores
Population-based study
MRI

SUMMARY

Objective: To establish sex-specific (subregional) reference values of cartilage thickness and potential maximal Z-scores in the femorotibial joint.
Methods: The mean cartilage thickness (ThCtAB.Me) in femorotibial compartments, plates and subregions was determined on coronal magnetic resonance imaging (MRI) from a population-based sample (Framingham) and from a healthy reference sample of the Osteoarthritis Initiative (OAI).
Results: 686 Framingham participants (309 men, 377 women, age 62 ± 8 years) had no radiographic femorotibial osteoarthritis (OA) ("normals") and 376 (156 men, 220 women) additionally had no MRI features of cartilage lesions ("supernormals"). The Framingham "normals" had thinner cartilage in the medial (3.59 mm) than in the lateral femorotibial compartment (3.86 mm). Medially, the femur displayed thicker cartilage (1.86 mm) than the tibia (1.73 mm), and laterally the tibia thicker cartilage (2.09 mm) than the femur (1.77 mm). The thickest cartilage was observed in central, and the thinnest in external femorotibial subregions. Potential maximal Z-scores ranged from 5.6 to 9.8 throughout the subregions; men displayed thicker cartilage but similar potential maximal Z-scores as women. Mean values and potential maximal Z-scores in Framingham "supernormals" and non-exposed OAI reference participants (112 participants without symptoms or risk factors of knee OA) were similar to Framingham "normals".
Conclusions: We provide reference values and potential maximal Z-scores of cartilage thickness in middle aged to elderly non-diseased populations without radiographic OA. Results were similar for "supernormal" participants without MRI features of cartilage lesions, and in a cohort without OA symptoms or risk factors. A cartilage thickness loss of around 27% is required for attaining a Z-score of −2.

Introduction

Cartilage morphology as determined quantitatively with magnetic resonance imaging (MRI) is being widely explored as a biomarker of disease status and progression in knee osteoarthritis (OA)[1–5]. Although an issue yet to be proven, it is also assumed that subjects with knee OA, whose cartilage thickness deviates from the normal range, may have a poorer prognosis than those whose cartilage thickness is in the normal range, and that the prognosis worsens as subjects progressively deviate from the normal range, eventually resulting in bone-to-bone contact. The cross-sectional evaluation of how much cartilage tissue has been lost at different stages of disease, however, requires reliable reference values from healthy subjects without knee OA, preferably from large population-based studies. Some investigators have provided mean values and standard deviations (SDs) from relatively small groups of normal healthy volunteers[6–10], but it remains unclear how representative these volunteers are with respect to the general population as to date, no values have been provided from large population-based studies. Recent longitudinal studies indicated that cartilage loss does not occur homogeneously throughout the femorotibial joint, but is greater in certain femorotibial subregions[11–14]. Therefore, it may be preferable to determine cartilage

* Address correspondence and reprint requests to: Felix Eckstein, Institute of Anatomy & Musculoskeletal Research, PMU, Strubergasse 21, A5020 Salzburg Austria. Tel: 43-662-44-2002-1240; Fax: 43-662-44-2002-1249.
E-mail address: felix.eckstein@pmu.ac.at (F. Eckstein).

1063-4584/$ – see front matter
doi:10.1016/j.joca.2010.07.010

differences at the subregional level in cross-sectional studies, requiring "reference values" also for specific femorotibial subregions[14,15].

The potential of estimating cartilage loss in cross-sectional studies is defined by (1) the difference between the mean values (for given femorotibial subregions) in a healthy reference population and "zero" (100% cartilage loss) and (2) the normal inter- or between-subject variability of the reference population. Z-scores or "standard" scores[8] indicate how many SDs an observation is above or below the mean of healthy subjects of the same age and sex. In the current context, therefore, Z-scores represent the difference between the measured cartilage thickness (in a patient) and the healthy cartilage thickness from a reference sample, divided by the between–subject SD in the healthy reference sample. The greater the cartilage thickness and the smaller the between-subject SD, the greater the maximal potential Z-score[8], and the greater the potential to detect whether a sample or a person studied cross-sectionally has indeed experienced cartilage loss. Although a cartilage thickness value of "zero" is a very unlikely event, even in end-stage knee OA, it is useful to explore which maximal Z-scores can be expected in different femorotibial compartments, plates, and subregions.

The primary objective of this paper was thus to establish sex-specific (subregional) reference values of normal femorotibial cartilage thickness (ThCtAB) from a large population-based cohort, and to determine the maximal potential (subregional) Z-scores for cross-sectional comparisons. Secondary objectives were to investigate to what extent selection of a "supernormal" group (no radiographic femorotibial OA and no MRI features of femorotibial cartilage lesions) produces reference values different from one that is considered "normal" based on radiographic evaluation alone. A related secondary objective was to explore whether the healthy sample from the OA Initiative cohort, which has not been exposed to risk factors for knee OA, displays values similar to those of the population-based study (Framingham) and can be used as an internal control for OAI participants with knee OA.

Methods

Framingham study sample

Participants were members of the Framingham OA Study Cohort[16–18]. This cohort consists of two subgroups: (1) members of the Framingham Heart Study Offspring study[19], a longitudinal population-based cohort study to examine risk factors for heart disease[20], and (2) a newly recruited community sample cohort from the town of Framingham, MA. Both subgroups were used in the current study. The first subgroup (Framingham Heart Study Offspring Cohort) has been described previously[21], and all active members of this group, whose parents had been studied for OA[22], received a letter of invitation and follow-up phone call for recruitment purposes. A validated survey instrument supplemented by questions about medication use was used to exclude persons with rheumatoid arthritis[23]. The second subgroup consisted of participants of the newly recruited community sample who were drawn from a random sample of the Framingham community. Subjects had to be aged 50–80 years, and ambulatory (use of assistive devices such as canes and walkers was allowed). Exclusion criteria were bilateral total knee replacements or rheumatoid arthritis as defined above and contraindications to MRI[23]. In neither of the two above groups were participants selected based on the presence or absence of knee OA, or risk factors of knee OA. Approval for the study in this combined group, designated the Framingham OA Study cohort, was obtained from the Boston University Medical Center Institutional Review Board and the participants were examined in 2002–2005[16–18]. The study protocol involved acquisition of posterior–anterior (PA) fixed flexion radiographs of both knees[24]. For the purpose of the current analysis, only participants with a femorotibial Kellgren Lawrence (KL) grade of 0[25] on PA views were included in the "normal" reference cohort.

MRI examinations of both knees were performed using a 1.5 Tesla (T) magnet (Siemens Symphony, Erlangen, Germany), unless one had a total knee prosthesis, in which case only one knee was imaged. In the Framingham Offspring subgroup, only participants reporting knee pain, aching or stiffness underwent MRI of the right knee, whereas MRIs were acquired in all members of the Community Cohort, regardless of symptom status.

For the purpose of semi-quantitative assessment of cartilage morphology, sagittal, coronal and axial proton density (PD)-weighted fat-suppressed images were acquired[18]. For the purpose of quantitatively measuring (subregional) cartilage morphology, coronal fast low angle shot sequences with water excitation (FLASHwe) were acquired with a 1.5 mm slice thickness and a 0.31 mm × 0.31 mm in-plane resolution in all right knees[17,18].

Osteoarthritis initiative (OAI) study sample

The OAI is a large ongoing cohort study, targeted at characterizing risk factors associated with the onset and progression of symptomatic knee OA, and at identifying biomarkers of the disease. Of the 4796 OAI participants, 122 represent a non-exposed healthy reference subcohort (public-use data set 0.F.1). The inclusion criteria for this subcohort are described on the OAI webpage (http://www.oai.ucsf.edu/datarelease/) and in Appendix 1; the participants had no symptoms or radiographic findings of knee OA, and no risk factors for knee OA (i.e., non-exposed cohort); they were 45–79 years old and included a diversity of ethnic minorities. General exclusion criteria (for all OAI participants) were rheumatoid or inflammatory arthritis, bilateral, end-stage knee OA, inability to walk without aids, and MRI contraindications.

The OAI imaging protocol included a coronal FLASHwe protocol with a spatial resolution identical to that used in the Framingham study, but acquired at 3T (Siemens Trio, Erlangen, Germany)[12,26–28]. From the 122 participants of the non-exposed reference subcohort, 112 had usable coronal FLASHwe acquisitions of the right knee.

Semi-quantitative cartilage scoring (Framingham sample)

In the Framingham (but not in the OAI) study sample, the whole-organ MRI scoring method (WORMS) described by Peterfy *et al.*[29] was used for semi-quantitative grading of articular cartilage integrity: 0 = normal thickness and signal; 1 = normal thickness but increased signal on PD-/T2-weighted images; 2 = partial-thickness focal defect <1 cm at its greatest width; 2.5 = full-thickness focal defect <1 cm at its greatest width; 3 = multiple areas of partial-thickness (grade 2) defects intermixed with areas of normal thickness, or a grade 2 defect wider than 1 cm but <75% of the region; 4 = diffuse (≥75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6 = diffuse (≥75% of the region) full-thickness loss. Cartilage was evaluated in 10 femorotibial regions: anterior, central, and posterior segments of the medial and lateral femur and tibia. Because the focus was on femorotibial cartilage, patello-femoral regions were not included.

Quantitative analysis of articular cartilage morphology

Segmentation of the femorotibial cartilage was performed using the coronal three-dimensional (3D) FLASHwe by readers from the same group in both the Framingham and in the OAI healthy reference sample[12,17,18,28]. These had received a formal training in cartilage segmentation using custom software (Chondrometrics GmbH). Manual tracing of the total subchondral bone area (tAB) and the cartilage joint surface area (AC) of the medial tibia (MT), lateral tibia (LT), central (weight-bearing) medial femoral condyle (cMF) and central (weight-bearing) lateral femoral condyle (cLF)[4,30,31] was performed, as well as quality control readings of all segmentations. Whereas the intercondylar bone bridge was used for defining the posterior end of the femoral (weight-bearing) region of interest in the Framingham study[32], a 60% criterion (distance from trochlear notch to posterior ends of the femoral condyles) was used in the OAI[30]. The segmentations were then used to compute the cartilage thickness over the entire subchondral bone area, including denuded areas as 0 mm cartilage thickness (ThCtAB)[4]. Results for the medial and lateral femorotibial compartments (MFTC/LFTC) were obtained by summing values of MT and cMF, and LT and cLF, respectively[31,33]. Then, five tibial subregions (central = cMT/cLT, internal = iMT/iLT, external = eMT/eLT, anterior = aMT/aLT, posterior = pMT/LT) were determined, with the central subregion occupying 20% of the tAB[15]. The weight-bearing femoral condyles were divided into three subregions (central = ccMF/ccLF, internal = icMF/icLF, and external = ecMF/ecLF), each occupying 33.3% of the tAB.

Statistical analysis

Descriptive statistics for femorotibial compartments, plates and subregions were given as mean ± SD ThCtAB in men and women separately, since previous studies have shown significant differences between sexes[9,34]. Potential maximal Z-scores (standard scores) were derived by dividing the difference between the mean value and zero by the inter-subject SD in each compartment, plate and subregion. Please note that the current paper does not report "observed" Z-scores for patients with knee OA, but computes theoretical (or "potential") maximal Z-scores, based on the normal distribution of cartilage thickness in various knee compartments, plates and subregions, under the assumption that the minimal cartilage thickness in these may attain values of "zero" in end-stage knee OA.

To test the hypothesis that the reference values for cartilage thickness from supernormal Framingham participants (without cartilage lesions apparent from semi-quantitative MRI scores) were different from normal (but not supernormal) Framingham participants (i.e., subjects with normal radiographs, but with cartilage lesions apparent from MRI), a regression model with mean outcome as a function of group assignment and covariates was applied. The comparison was adjusted for differences in age, height, and weight; differences between groups were considered to be significant if $P < 0.01$ (in view of the relatively large sample and in order to minimize the number of false positive comparisons), but no adjustment for multiple comparisons was made. The hypothesis that the mean values for cartilage thickness in the OAI non-exposed reference cohort were different from that in the population-based Framingham normal cohort was tested in the same way as described above.

Results

Demographics

From 2306 subjects investigated in the Framingham cohort, 1080 received MRI acquisitions of at least one knee. Of those, 686 (309 men, 377 women) had no sign of radiographic femorotibial OA in PA radiographic views and were considered a "normal" reference group. Subject characteristics are given in Table I.

310 (153 men, 157 women) of the 686 Framingham "normals" displayed MRI-based features of cartilage lesions (i.e., a WORMS cartilage score >0 [$n = 289$], a denuded subchondal bone area in the quantitative analysis [$n = 30$], or both [$n = 9$] in any weight-bearing femorotibial cartilage plate). The 376 participants without these features (156 men; 220 women) were considered a "supernormal" reference group. There was no significant difference in the subject characteristics of "supernormal" ($n = 220$) and non-supernormal women ($n = 157$). The supernormal men ($n = 156$) were significantly younger (Table I) than the non-supernormal men ($n = 153$). Of the 112 subjects in the non-exposed OAI subcohort, 43 were men and 69 women. Both the men and women were significantly younger and had a significantly lower body weight and BMI than the same sex Framingham normals; the women also were significantly taller than the Framingham participants (Table I).

Cartilage thickness reference values and Z-scores in Framingham normals

Averaging values of men and women in 686 Framingham normals, the cartilage in the MFTC (3.59 mm) was somewhat thinner than that in the lateral compartment (3.86 mm; Fig. 1), whilst the SD of the thickness was similar for both compartments. Medially, the femur (cMF) displayed a somewhat greater cartilage thickness (1.86 mm) than the tibia (MT, 1.73 mm), but laterally the tibia (LT) had thicker cartilage (2.09 mm) than the femur (cLF, 1.77 mm). In all femorotibial plates the central subregions displayed thicker cartilage than the peripheral subregions; the cartilage was thinnest in the external subregions (Fig. 1). cLT displayed the thickest cartilage (3.13 mm), and ecMF the thinnest cartilage (1.37 mm) across all subregions (Fig. 1).

The men displayed thicker cartilage thickness than women (Table II, Fig. 2) throughout all plates and subregions. Histograms of the cartilage thickness distribution in the MT of men and women, respectively, are displayed in Fig. 3. In men, the maximal Z-scores for compartments, plates and subregions ranged from 6.1 (ecMF) to 9.8 (LFTC), and in women from 5.6 (ccMF) to 9.3 (LFTC). When averaged across compartments, plates and subregions, the maximal Z-scores were similar in men (7.5) and women (7.3).

Table I
Subject characteristics of the population-based Framingham cohort and of the OAI non-exposed reference cohort

		Framingham normal		Framingham supernormal		OAI	
Men		$n = 309$		$n = 156$		$n = 43$	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
	Age	62.9	8.8	60.3*	7.4	57.0†	9.6
	Height	174.6	7.5	174.3	7.6	174.9	6.9
	Weight	86.3	14.7	86.0	14.8	79.3†	8.2
	BMI	28.3	4.3	28.3	4.5	26.1†	3.0
Women		$n = 377$		$n = 220$		$n = 69$	
	Age	61.7	7.9	61.2	7.8	53.8†	6.0
	Height	160.8	6.7	160.7	6.7	163.5†	6.5
	Weight	71.6	15.6	71.0	15.8	61.9†	8.2
	BMI	27.7	5.8	27.5	5.9	23.1†	2.5

* Significantly different compared with those of the Framingham normal cohort that were not supernormal ($n = 153$) at $P < 0.01$.
† Significantly different compared with those of the Framingham normal cohort ($n = 309$) at $P < 0.01$.

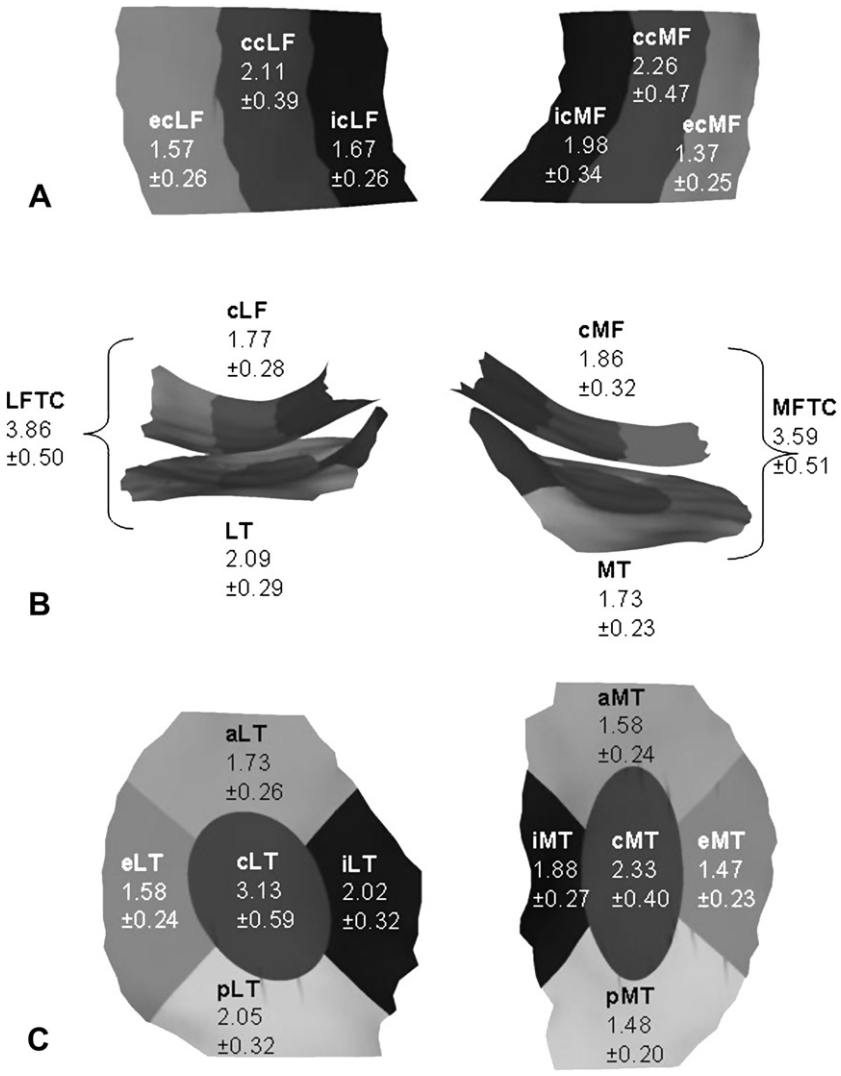

Fig. 1. Schematic showing (A) View of the central (weight-bearing) femoral condyles (cMF/cLF) from inferior, (B) View of the central (weight-bearing) femoral condyles (cMF/cLF) and tibiae (MT/LT) from posterior, (C) View of the tibiae (MT/LT) from superior. Mean values and SDs of cartilage thickness (ThCtAB, averaged for men and women) from 686 normal subjects (KL grade 0) of the Framingham cohort are shown for femorotibial compartments, plates and subregions: MFTC = MT + cMF, LFTC = LT + cLF; subregion labels: c = central, e = external, i = internal, a = anterior, p = posterior.

Cartilage thickness reference values and Z-scores in Framingham supernormals

Mean thickness values in the Framingham supernormals (Table III) were within 0.06 mm (2.6%) of those in Framingham normals across all compartments, plates and subregions (Table II, Fig. 2). The differences ranged from −0.06 mm and −2.6% (both ccLF) to +0.05 mm (cLT) and +1.9% (pLT) in men, and from −0.05 mm and −2.5% (both ccLF) to +0.03 mm (cLT) and +1.0% (pLT) in women (Table III). Across the 22 subregions, 14 had smaller values in Framingham "supernormals" compared with normals, and eight showed larger or the same values (men and women). When comparing the results in the supernormals with non-supernormals, the only plate with significant differences was cLF in women (Table III, Fig. 2). No subregion in the supernormal men showed significantly different values from non-supernormal normals after adjustment for age, weight, and height, but two subregions in supernormal women did (ccLF, icLF; Table III). The maximal Z-scores were similar in supernormals (7.6 in men, 7.8 in women) and non-supernormal Framingham normals (7.5 and 7.3), when being averaged across compartments, plates and subregions.

Cartilage thickness reference values and Z-scores in non-exposed OAI participants

The mean cartilage thickness (ThCtAB.Me) values in the non-exposed OAI subcohort (Table IV) were also similar to the Framingham normals (Table II), with differences of less than 0.2 mm and 8.2% in all compartments, plates and subregions. The differences ranged from −0.09 mm (MFTC) and −5.3% (ecLF) to +0.19 mm (cLT) and +7.6% (eLT) in men, and from −0.15 mm and −7.6% (both pLT) to +0.12 mm and +8.2% (both eLT) in women. Across the 22 cartilage regions, 14 displayed smaller and eight greater values in male OAI participants compared with Framingham normals. Nine of the 22 regions displayed smaller values, nine greater values, and four the same values in female OAI participants compared with Framingham normals (Table III). There were no significant differences in cartilage plates or compartments between the non-exposed OAI and the Framingham participants, but one subregion (eLT; Table IV) in OAI men and three subregions in OAI women (eLT, aLT, pLT; Table IV) showed values significantly different from Framingham normals. In men, the maximal Z-scores for compartments and plates ranged from 7.1 (cMF) to 9.7 (LFTC),

Table II
Framingham normal cohort ($n = 686$); participants without radiographic femorotibial OA (KL grade 0): Mean values (mean), 95% confidence interval (CI) of the mean SD and Max Z-score for ThCtAB.Me in femorotibial cartilage plates and subregions

Region	Men			Women		
	Mean (95% CI)	SD	Max Z-score	Mean (95% CI)	SD	Max Z-score
MT	1.86 (1.84–1.89)	0.21	8.8	1.62 (1.61–1.64)	0.18	9.1
cMF	2.06 (2.03–2.10)	0.29	7.2	1.70 (1.67–1.72)	0.24	6.9
MFTC	3.93 (3.88–3.98)	0.45	8.7	3.32 (3.28–3.36)	0.39	8.6
LT	2.25 (2.22–2.28)	0.26	8.7	1.95 (1.93–1.98)	0.24	8.1
cLF	1.93 (1.90–1.96)	0.25	7.7	1.65 (1.63–1.67)	0.23	7.1
LFTC	4.19 (4.14–4.24)	0.43	9.8	3.61 (3.57–3.65)	0.39	9.3
cMT	2.54 (2.49–2.58)	0.39	6.6	2.17 (2.13–2.20)	0.31	6.9
eMT	1.59 (1.57–1.62)	0.22	7.3	1.36 (1.34–1.38)	0.18	7.8
iMT	2.01 (1.98–2.04)	0.27	7.6	1.77 (1.75–1.79)	0.22	8.1
aMT	1.73 (1.70–1.75)	0.21	8.2	1.46 (1.44–1.48)	0.19	7.6
pMT	1.54 (1.52–1.57)	0.22	7.1	1.43 (1.41–1.45)	0.17	8.3
ccMF	2.54 (2.49–2.59)	0.44	5.7	2.05 (2.01–2.09)	0.37	5.6
ecMF	1.51 (1.48–1.53)	0.25	6.1	1.26 (1.24–1.28)	0.20	6.4
icMF	2.19 (2.15–2.23)	0.30	7.2	1.83 (1.80–1.85)	0.27	6.8
cLT	3.44 (3.38–3.50)	0.53	6.6	2.87 (2.82–2.93)	0.51	5.7
eLT	1.71 (1.68–1.73)	0.22	7.7	1.47 (1.45–1.49)	0.21	7.1
iLT	2.19 (2.16–2.22)	0.28	7.7	1.89 (1.86–1.91)	0.27	7.0
aLT	1.87 (1.84–1.90)	0.26	7.3	1.62 (1.60–1.64)	0.21	7.7
pLT	2.13 (2.09–2.17)	0.32	6.7	1.98 (1.95–2.01)	0.31	6.4
ccLF	2.30 (2.25–2.34)	0.36	6.4	1.97 (1.93–2.00)	0.34	5.8
ecLF	1.70 (1.68–1.73)	0.24	7.2	1.46 (1.43–1.48)	0.22	6.8
icLF	1.83 (1.80–1.86)	0.23	7.8	1.55 (1.53–1.58)	0.21	7.3

Please note that this table does not report "observed" Z-scores for patients with knee OA, but computes theoretical maximal Z-scores based on the normal distribution of cartilage thickness in various knee compartments, plates and subregions, under the assumption that the minimal cartilage thickness in these may attain values of "zero" in end-stage knee OA.

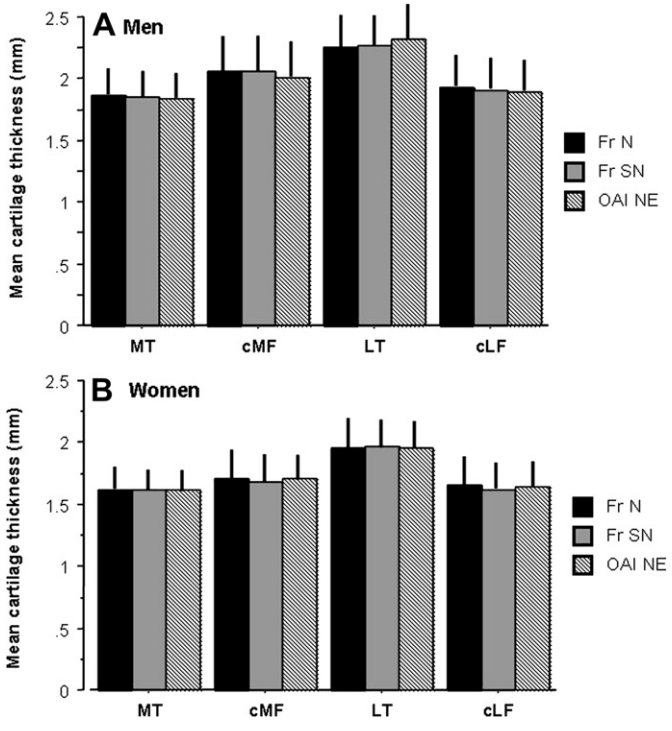

Fig. 2. Bar graphs showing the mean and SD of cartilage thickness of the femorotibial cartilage plates in Framingham "normals" (no radiographic femorotibial OA), in Framingham "supernormals" (no radiographic femorotibial OA and no MRI features of cartilage lesions), and in non-exposed OAI reference cohort (no radiographic femorotibial OA, no symptoms of risk factors of knee OA) (A) Cartilage thickness in men (B) Cartilage thickness in women.

and in women from 8.2 (cLF) to 10.2 (LFTC). Amongst femorotibial subregions, maximal Z-scores in men ranged from 6.0 (ccMF) to 10.0 (iMT), and in women from 6.4 (cLT) to 8.8 (eLT). The Z-scores were very similar in non-exposed OAI participants (7.6 in men, 8.1 in women) compared with Framingham normals (7.5 and 7.3), when averaged across compartments, plates and subregions.

Discussion

The primary objectives of this study were to establish (sex-specific, subregional) reference values of femorotibial cartilage thickness (ThCtAB) from a large population-based cohort. Key findings are that medially the femur displayed thicker cartilage than the tibia, whereas laterally, the opposite was the case. The thickest cartilage was found in the central subregion of the LT [cLT], and the thinnest in the external subregions of the weight-bearing medial femur [ecMF]. Men displayed thicker cartilage than women throughout all plates and subregions, but the maximal Z-scores were similar between men in women. The values derived from "supernormal" participants (with no MRI features of femorotibial cartilage lesions in addition to normal femorotibial radiographs) were within 0.06 mm (2.6%) of those in the "normal" subjects (KL grade 0), and Z-scores were similar to those obtained form normals. The mean values for the non-exposed OAI reference cohort were within 0.2 mm (8.2%) of those of the Framingham normals, and again the Z-scores were very similar for all compartments, plates and subregions.

A potential limitation of the current study is the use of a 1.5T protocol in the Framingham and the use of a 3T protocol in the OAI cohort. However, a previous study that compared measurements at 1.5T and 3T face-to-face showed high agreement and no systematic deviation of the cartilage thickness between different field strengths[35]. Also, the two studies involved somewhat different definitions of the femoral region of interest analyzed intercondylar bone bridge [=short ROI] in the Framingham study; 60% criterion [=long ROI] in the OAI. A recent analysis[36] that compared both ROIs directly in the same subjects, however, revealed that there were no systematic differences in cartilage thickness between the short and long femoral ROI, respectively.

Another limitation of this study is that the subregions, as described and defined here[12,15] are currently not widely used by the scientific community. However, the subregions are based on standard anatomical directions and thus represent aspects of the joint surfaces that other investigators can easily refer to. Also, one must keep in mind that three components contribute to the measured SD: the variance between individuals, the day-to-day variation in cartilage due, for example, to small differences in previous loading or hydration, and the precision errors arising from segmentation error and scanner noise. The SD reported here was 10–18% of the mean, whereas precision errors reported in the literature ranged from 1.5 to 3%, even when measurement were performed on different days[5,37]. Therefore the reported SDs should mainly reflect inter-subject variability.

Amongst different morphological parameters, the ThCtAB.Me over the entire subchondral bone area (including denuded areas [ThCtAB][4]) determined in the current study, was previously found to better discriminate between patients scheduled for knee arthroplasty or tibial osteotomy and normal volunteers than cartilage volume[8]. ThCtAB is conceptionally the same as normalized cartilage volume (volume divided by the tAB)[4,8] and can be computed for total cartilage plates and various subregions[15]. Recent cross-sectional studies found, however, surprisingly little difference in cartilage thickness between supposedly normal subjects and participants with various grades of mild radiographic OA[18,38]. The finding of greater lateral (LT) than medial tibial (MT) cartilage

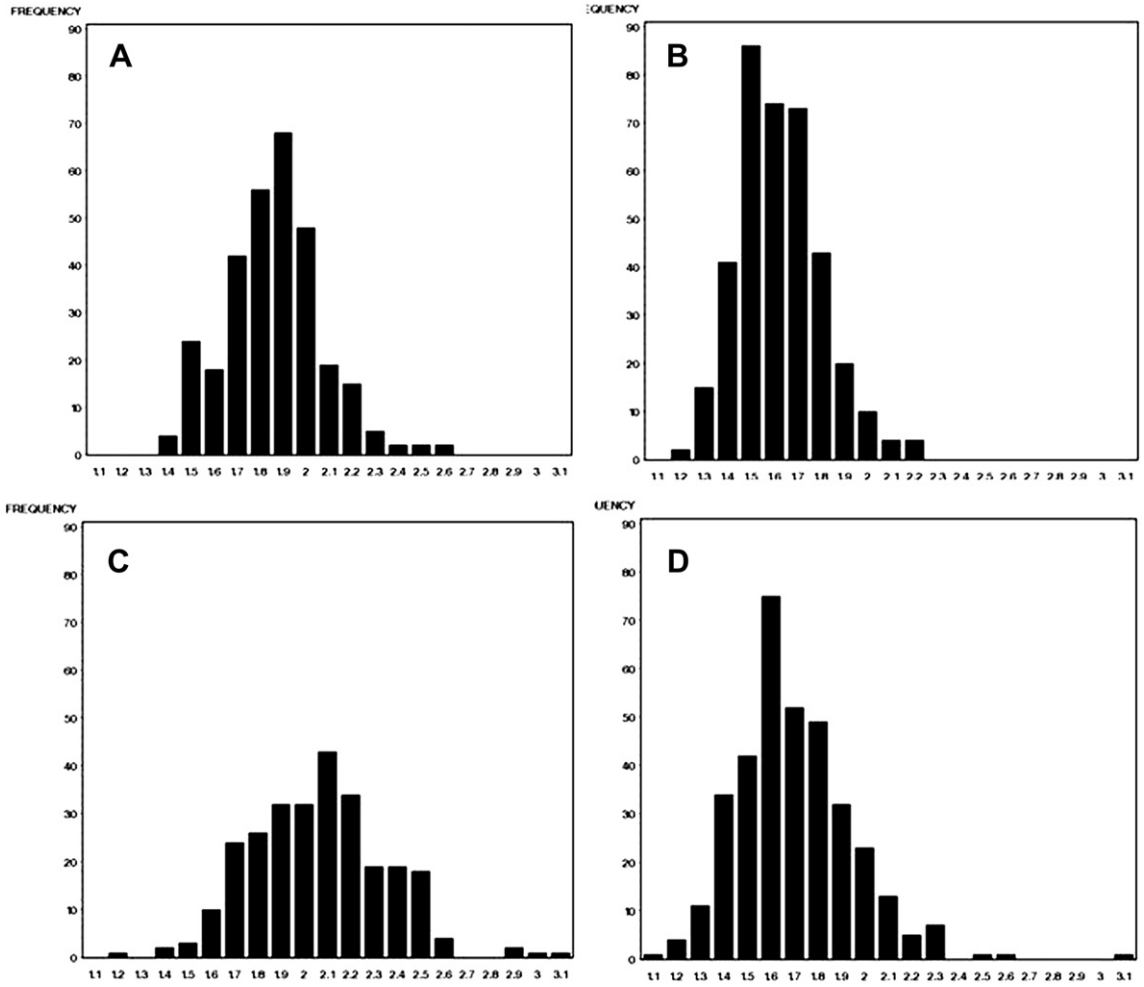

Fig. 3. Representative histograms of the cartilage thickness distribution in the MT and cMF from the Framingham cohort. (A) MT cartilage thickness distribution in men (B) MT cartilage thickness distribution in women (C) cMF cartilage thickness distribution in men (D) cMF cartilage thickness distribution in women.

thickness (ThCtAB) has been previously reported in a reference cohort of young adults aged 20–35 years[8]. In a smaller study of female participants aged >40 years, the same pattern of ThCtAB.Me values (greater in lateral than in MT, greater in medial femur than in MT, greater in LT than in lateral femur), and greater in medial femur than in medial tibia). This is the first study, however, to report subregional reference values for cartilage thickness in both men and women.

An interesting observation from the current study is that, although 45% of the Framingham participants with normal PA radiographs (KL grade 0) displayed signs of femorotibial cartilage lesions on MRI, exclusion of these participants did not affect the mean thickness values or maximal potential Z-scores. If anything, the cartilage thickness in "supernormals" (normal femorotibial radiographs and no MRI features of femorotibial cartilage lesions) was less than in participants displaying normal X-rays but also MRI cartilage lesions. Presence of WORMS scores >0 or denuded areas in cases where radiographs are normal thus does not appear to be associated with a reduction in mean cartilage thickness throughout subregions or plates. A recent paper from the Framingham cohort showed that even participants with early radiographic OA did not display systematically thinner cartilage than radiographically normal participants, but significantly higher WORMS cartilage scores[18]. On the contrary, there is some recent evidence from cross-sectional[38] and longitudinal[39] studies that the cartilage may undergo thickening (swelling or hypertrophy) at the early phase of radiographic OA, and this may be a reason for the "supernormals" to exhibit thinner cartilage than participants with pre-radiographic cartilage lesions. For establishing reference values of cartilage thickness in certain populations, however, it appears to be sufficient to study participants with normal radiographs.

Similarly, the non-exposed OAI healthy reference cohort displayed very similar ThCtAB.Me values and Z-scores compared with Framingham participants, despite the somewhat younger age and smaller BMI, and the lack of risk factors for knee OA. These results indicate that, as published previously[10], knee cartilage thickness in healthy subjects is independent of age, and that the presence/absence of risk factors may not be associated with differences in cartilage thickness, as long as the X-rays are normal. Also, the results confirm that the non-exposed reference cohort from the OAI can be used as an internal control in cross-sectional studies comparing disease-specific differences in cartilage thickness within the OAI cohort.

T-scores (comparison with young healthy subjects) and Z-scores (comparison with healthy subjects of similar age) are frequently used in the diagnostics of osteoporotic bone loss, Burgkart *et al.*[8] and reported only moderate Z-scores (around

Table III
Framingham supernormal cohort ($n = 376$); participants without radiographic femorotibial OA and without MRI features of femorotibial cartilage lesions (WORMS cartilage scores 0, and no denuded areas in quantitative MRI): Mean values (mean), 95% CI of the mean SD and maximal potential Z-scores (max Z-score) for ThCtAB.Me in femorotibial cartilage plates and subregions

Region	Men			Women		
	Mean (95% CI)	SD	Max Z-score	Mean (95% CI)	SD	Max Z-score
MT	1.85 (1.82–1.88)	0.21	9.0	1.62 (1.60–1.64)	0.17	9.4
cMF	2.06 (2.02–2.11)	0.29	7.1	1.68 (1.65–1.71)	0.22	7.8
MFTC	3.91 (3.84–3.99)	0.46	8.5	3.30 (3.25–3.35)	0.35	9.5
LT	2.27 (2.23–2.31)	0.24	9.3	1.96 (1.93–1.99)	0.23	8.5
cLF	1.90 (1.86–1.94)	0.25	7.6	1.62* (1.59–1.65)	0.21	7.8
LFTC	4.17 (4.10–4.24)	0.42	9.9	3.58 (3.53–3.63)	0.35	10.2
cMT	2.52 (2.46–2.58)	0.37	6.9	2.15 (2.11–2.19)	0.30	7.2
eMT	1.59 (1.56–1.63)	0.22	7.4	1.36 (1.33–1.38)	0.17	7.9
iMT	1.98 (1.94–2.02)	0.26	7.6	1.76 (1.73–1.79)	0.21	8.5
aMT	1.72 (1.68–1.75)	0.21	8.1	1.46 (1.43–1.48)	0.19	7.7
pMT	1.53 (1.50–1.56)	0.22	7.1	1.43 (1.41–1.46)	0.17	8.4
ccMF	2.54 (2.47–2.61)	0.42	6.0	2.03 (1.98–2.08)	0.33	6.2
ecMF	1.49 (1.45–1.53)	0.26	5.8	1.23 (1.21–1.26)	0.17	7.1
icMF	2.21 (2.16–2.26)	0.31	7.2	1.82 (1.78–1.85)	0.25	7.3
cLT	3.49 (3.41–3.57)	0.49	7.2	2.90 (2.83–2.96)	0.47	6.2
eLT	1.69 (1.65–1.72)	0.23	7.4	1.46 (1.44–1.49)	0.20	7.4
iLT	2.22 (2.18–2.27)	0.28	8.0	1.90 (1.87–1.93)	0.25	7.7
aLT	1.86 (1.82–1.90)	0.25	7.5	1.61 (1.58–1.63)	0.21	7.8
pLT	2.17 (2.13–2.22)	0.30	7.2	2.00 (1.96–2.04)	0.30	6.6
ccLF	2.24 (2.18–2.30)	0.35	6.4	1.92* (1.88–1.96)	0.30	6.4
ecLF	1.67 (1.64–1.71)	0.23	7.2	1.43 (1.41–1.46)	0.19	7.5
icLF	1.80 (1.77–1.84)	0.23	7.7	1.53* (1.50–1.56)	0.20	7.7

* Significantly different compared with those of the Framingham normal cohort that were not supernormal ($n = 153$) at $P < 0.01$; comparisons were adjusted for differences in age, height, and weight. Cartilage plate and compartment labels MT = medial tibia, cMF = central (weight-bearing) medial femur, MFTC = medial femorotibial compartment = MT+cMF, LT = lateral tibia, cLF = central (weight-bearing) lateral femur, LFTC = lateral femorotibial compartment = LT+cLF; subregion labels: c = central, e = external, i = internal, a = anterior, p = posterior.

Table IV
OAI non-exposed cohort, without femorotibial radiographic OA (KL grade 0) or symptoms or risk factors of knee OA

Region	Men			Women		
	Mean (95% CI)	SD	Max Z-score	Mean (95% CI)	SD	Max Z-score
MT	1.83 (1.77–1.89)	0.20	9.1	1.62 (1.58–1.66)	0.17	9.7
cMF	2.01 (1.92–2.10)	0.28	7.1	1.71 (1.66–1.75)	0.20	8.3
MFTC	3.84 (3.71–3.98)	0.43	8.9	3.33 (3.25–3.41)	0.33	10.0
LT	2.32 (2.24–2.41)	0.27	8.6	1.95 (1.90–2.00)	0.22	8.9
cLF	1.89 (1.81–1.97)	0.25	7.4	1.64 (1.59–1.68)	0.20	8.2
LFTC	4.21 (4.08–4.35)	0.43	9.7	3.59 (3.50–3.67)	0.35	10.2
cMT	2.56 (2.44–2.67)	0.37	6.9	2.24 (2.17–2.31)	0.29	7.7
eMT	1.60 (1.54–1.67)	0.22	7.2	1.37 (1.33–1.41)	0.16	8.5
iMT	1.97 (1.91–2.03)	0.20	10.0	1.77 (1.71–1.82)	0.22	7.9
aMT	1.65 (1.59–1.71)	0.20	8.4	1.39 (1.35–1.44)	0.18	7.7
pMT	1.49 (1.42–1.56)	0.22	6.7	1.42 (1.38–1.46)	0.17	8.5
ccMF	2.49 (2.36–2.61)	0.41	6.1	2.09 (2.01–2.15)	0.29	7.3
ecMF	1.43 (1.37–1.49)	0.20	7.0	1.23 (1.19–1.27)	0.17	7.3
icMF	2.14 (2.04–2.23)	0.31	6.9	1.82 (1.76–1.87)	0.23	7.8
cLT	3.63 (3.45–3.80)	0.57	6.4	2.98 (2.87–3.09)	0.47	6.4
eLT	1.84* (1.77–1.90)	0.22	8.4	1.59* (1.55–1.64)	0.18	8.8
iLT	2.28 (2.19–2.37)	0.28	8.0	1.88 (1.81–1.94)	0.28	6.8
aLT	1.88 (1.79–1.97)	0.28	6.7	1.54* (1.49–1.59)	0.20	7.6
pLT	2.07 (1.98–2.17)	0.30	6.8	1.83* (1.77–1.90)	0.26	7.0
ccLF	2.27 (2.15–2.38)	0.38	6.0	1.99 (1.92–2.06)	0.29	6.8
ecLF	1.63 (1.55–1.70)	0.24	6.8	1.38 (1.34–1.42)	0.17	8.2
icLF	1.80 (1.73–1.87)	0.23	7.7	1.57 (1.51–1.62)	0.20	7.8

Mean values (mean), 95% CI of the mean SD and max Z-score for ThCtAB.Me in femorotibial cartilage plates and subregions.

* Significantly different compared with those of the Framingham normal cohort ($n = 309$) at $P < 0.01$. Comparisons were adjusted for differences in age, height, and weight. Cartilage plate and compartment labels MT = medial tibia, cMF = central (weight-bearing) medial femur, MFTC = medial femorotibial compartment = MT+cMF, LT = lateral tibia, cLF = central (weight-bearing) lateral femur, LFTC = lateral femorotibial compartment = LT+cLF; subregion labels: c = central, e = external, i = internal, a = anterior, p = posterior.

−1.0) in participants scheduled for correction osteotomy, and higher scores (around −3.8) in participants scheduled for total knee arthroplasty. The potential maximal Z-scores (computed by dividing the difference between the mean and zero by the inter-subject SD of cartilage thickness in the participants) in the current study ranged from 5.7 to 10.2 across cohorts/compartments/plates/subregions, and were 7.4, on average, in Framingham normals. These results indicate that a cartilage thickness loss of around 27% is required to attain a Z-score of −2.0. Cartilage thickness reductions of up to 20% in the medial femorotibial cartilage plates have been observed in a cross-sectional comparison of participants with medial JSN compared with a healthy reference cohort[38], suggesting that the Z-scores of cartilage thickness loss observed in OA are only moderate.

In conclusion, this paper shows consistent mean values, maximal Z-scores, and patterns of cartilage thickness in the femorotibial joint across “normal” and “supernormal” participants of the population-based Framingham cohort and the non-exposed reference cohort of the OAI. Although 45% of the Framingham participants with normal radiographs showed MRI features of femorotibial cartilage lesions, exclusion of these participants did not significantly affect mean values or maximal Z-scores for cartilage thickness. Likewise, examination of a reference cohort without risk factors of knee OA (the non-exposed OAI reference cohort) produced values consistent with those from the population-based Framingham cohort. Normal femorotibial radiographs thus appear to be a sufficient inclusion criterion for establishing reference values for femorotibial cartilage thickness. The results indicate that a cartilage thickness loss of around 27% is required for attaining a Z-score of −2.

Authors’ contribution

All authors have made substantial contributions to: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

F.E. (felix.eckstein@pmu.ac.at) and D.F. (dfelson@bu.edu) take responsibility for the integrity of the work as a whole, from inception to finished article.

F.E. was involved in conception and design of the study, obtaining of funding, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

M.Y. was involved in statistical analysis, assembly of the data, analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article.

A.G. was involved in the analysis (semi-quantitative scoring) and interpretation of the data, collection and assembly of the data, critical revision of the article for important intellectual content, and final approval of the article.

F.R. was involved in the acquisition, analysis (semi-quantitative scoring) and interpretation of the data, assembly of the data, critical revision of the article for important intellectual content, and final approval of the article.

M.H. was involved in the analysis (quality control readings) and interpretation of the data, assembly of the data, critical revision of the article for important intellectual content, and final approval of the article.

K.P. was involved in conception and design of the study, obtaining of funding, critical revision of the article for important intellectual content, and final approval of the article.

F.B. was involved in conception and design of the study, obtaining of funding, critical revision of the article for important intellectual content, and final approval of the article.

W.W. was involved in the analysis (computation of quantitative cartilage morphometry outcomes) and interpretation of the data, assembly of the data, critical revision of the article for important intellectual content, and final approval of the article.

D.F. was involved in conception and design of the study, obtaining of funding, acquisition, analysis and interpretation of the data, logistical support, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

Conflict of interest

- Felix Eckstein is CEO and co-owner of Chondrometrics GmbH. He provides consulting services to MerckSerono, Pfizer, Wyeth and Novartis.
- Mei Yang has no competing interests.
- Ali Guermazi is CEO and co-owner of Boston Imaging Core Lab, LLC (BICL) and owns stocks/or stock options in Synarc. He provides consulting services to MerckSerono, Stryker and Facet Solutions.
- Frank Roemer and co-owner of Boston Imaging Core Lab, LLC (BICL).
- Kristen Picha has a full time employment with Centocor R&D, Inc.
- Frédéric Baribaud has a full time employment with Centocor R&D, Inc.
- Martin Hudelmaier has a part time employment with Chondrometrics GmbH.
- Wolfgang Wirth has a part time employment with Chondrometrics GmbH.
- David Felson has no competing interests.

Acknowledgment

We would like to thank and Jingbo Niu and Xiang Zheng, Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, MA, for their help with the statistical analysis, and Piran Aliabadi, Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts for performing the readings of the radiographs in the Framingham study. We also would like to thank the following operators who performed the cartilage segmentations in the Framingham and OAI reference cohorts: Gudrun Goldmann, Linda Jakobi, Manuela Kunz, Dr Susanne Maschek, Jana Matthes, Sabine Mühlsimer, Annette Thebis, and Dr Barbara Wehr. The study, image acquisition and image analysis for the Framingham cohort were funded by NIH AG18393 and AR47785 grants. The study and image acquisition for the Osteoarthritis initiative non-exposed reference cohort was funded through a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262). The image analysis for the Osteoarthritis initiative non-exposed reference cohort was funded by Centocor Inc. The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

Appendix 1. (to be published online)

The OAI participants were recruited at four clinical sites: the University of Maryland School of Medicine (Baltimore), the Ohio State University (Columbus), the University of Pittsburgh, and the Memorial Hospital of Rhode Island (Pawtucket). Participants of the non-exposed healthy reference cohort (0.B.1.) had

- No pain, aching or stiffness in either knee in the past year.
- No radiographic findings of femorotibial OA (Osteoarthritis Research Society International (OARSI) osteophyte grade 0 and joint space narrowing grade 0) of either knee using the clinic reading of the baseline bilateral fixed flexion radiographs[24]. Radiographic findings in a lateral (patello-femoral) view of the knees were not used to determine eligibility for this group.
- No risk factors for the onset of knee OA, including
  - Obesity defined as a body weight of >170 lbs (77.1 kg) in women aged 45–69, >180 lbs (81.7 kg) in women aged 70–79, >205 lbs (93 kg) in men aged 45–69, and >215 lbs (97.5 kg) in men aged 70–79.
  - History of knee injury, defined as having caused difficulty walking for at least a week.
  - Knee surgery.
  - Family history of total knee replacement in a biological parent or sibling.
  - Heberden's nodes, defined as self-reported bony enlargements of one or more distal interphalangeal joints in both hands.
  - Repetitive knee bending, defined as current daily activity at work or outside work, requiring frequent climbing, stooping, bending, lifting, squatting or kneeling.

References

1. Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H, *et al*. Imaging in osteoarthritis. Rheum Dis Clin North Am 2008;34:645–87.
2. Eckstein F, Mosher T, Hunter D. Imaging of knee osteoarthritis: data beyond the beauty. Curr Opin Rheumatol 2007;19: 435–43.
3. Eckstein F, Burstein D, Link TM. Quantitative MRI of cartilage and bone: degenerative changes in osteoarthritis. NMR Biomed 2006;19:822–54.
4. Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, *et al*. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage 2006;14: 974–83.
5. Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfy C. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. Osteoarthritis Cartilage 2006;14(Suppl 1):46–75.
6. Eckstein F, Winzheimer M, Westhoff J, Schnier M, Haubner M, Englmeier KH, *et al*. Quantitative relationships of normal cartilage volumes of the human knee joint–assessment by magnetic resonance imaging. Anat Embryol (Berl) 1998;197: 383–90.
7. Hudelmaier M, Glaser C, Englmeier KH, Reiser M, Putz R, Eckstein F. Correlation of knee-joint cartilage morphology with muscle cross-sectional areas vs. anthropometric variables. Anat Rec 2003;270A:175–84.
8. Burgkart R, Glaser C, Hinterwimmer S, Hudelmaier M, Englmeier KH, Reiser M, *et al*. Feasibility of T and Z scores from magnetic resonance imaging data for quantification of cartilage loss in osteoarthritis. Arthritis Rheum 2003;48:2829–35.

9. Otterness IG, Eckstein F. Women have thinner cartilage and smaller joint surfaces than men after adjustment for body height and weight. Osteoarthritis Cartilage 2007;15:666–72.
10. Beattie KA, Duryea J, Pui M, O'Neill J, Boulos P, Webber CE, *et al*. Minimum joint space width and tibial cartilage morphology in the knees of healthy individuals: a cross-sectional study. BMC Musculoskelet Disord 2008;9:119.
11. Pelletier JP, Raynauld JP, Berthiaume MJ, Abram F, Choquette D, Haraoui B, *et al*. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. Arthritis Res Ther 2007;9. R74.
12. Wirth W, Hellio Le Graverand MP, Wyman BT, Maschek S, Hudelmaier M, Hitzl W, *et al*. Regional analysis of femorotibial cartilage loss in a subsample from the osteoarthritis initiative progression subcohort. Osteoarthritis Cartilage 2009;17:291–7.
13. Le Graverand MP, Buck RJ, Wyman BT, *et al*. Change in regional cartilage morphology and joint space width in osteoarthritis participants versus healthy controls: a multicentre study using 3.0 Tesla MRI and Lyon-Schuss radiography. Ann Rheum Dis 2010;69(1):155–62.
14. Eckstein F, Guermazi A, Roemer FW. Quantitative MR imaging of cartilage and trabecular bone in osteoarthritis. Radiol Clin North Am 2009;47:655–73.
15. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Trans Med Imaging 2008;27:737–44.
16. Lo GH, Hunter DJ, Zhang Y, McLennan CE, LaValley MP, Kiel DP, *et al*. Bone marrow lesions in the knee are associated with increased local bone density. Arthritis Rheum 2005;52:2814–21.
17. Hunter DJ, Niu JB, Zhang Y, LaValley M, McLennan CE, Hudelmaier M, *et al*. Premorbid knee osteoarthritis is not characterised by diffuse thinness: the Framingham Osteoarthritis Study. Ann Rheum Dis 2008;67:1545–9.
18. Reichenbach S, Yang M, Eckstein F, Niu J, Hunter DJ, McLennan CE, *et al*. Do cartilage volume or thickness distinguish knees with and without mild radiographic osteoarthritis? The Framingham Study. Ann Rheum Dis 2009.
19. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med 1975;4:518–25.
20. Dawber TR, Meadors GF, Moore Jr FE. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health 1951;41:279–81.
21. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
22. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914–8.
23. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, *et al*. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol 1995;5:297–302.
24. Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, *et al*. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. Skeletal Radiol 2003;32:128–32.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
26. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433–41.
27. Hunter DJ, Niu J, Zhang Y, Totterman S, Tamez J, Dabrowski C, *et al*. Change in cartilage morphometry: a sample of the progression cohort of the osteoarthritis initiative. Ann Rheum Dis 2009;68:349–56.
28. Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, *et al*. One year change of knee cartilage morphology in the first release of participants from the osteoarthritis initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. Ann Rheum Dis 2009;68:674–9.
29. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al*. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
30. Eckstein F, Hudelmaier M, Wirth W, Kiefer B, Jackson R, Yu J, *et al*. Double echo steady state magnetic resonance imaging of knee articular cartilage at 3 Tesla: a pilot study for the osteoarthritis initiative. Ann Rheum Dis 2006;65:433–41.
31. Eckstein F, Kunz M, Hudelmaier M, Jackson R, Yu J, Eaton CB, *et al*. Impact of coil design on the contrast-to-noise ratio, precision, and consistency of quantitative cartilage morphometry at 3 Tesla: a pilot study for the osteoarthritis initiative. Magn Reson Med 2007;57:448–54.
32. Glaser C, Burgkart R, Kutschera A, Englmeier KH, Reiser M, Eckstein F. Femoro-tibial cartilage metrics from coronal MR image data: technique, test-retest reproducibility, and findings in osteoarthritis. Magn Reson Med 2003;50:1229–36.
33. Eckstein F, Kunz M, Schutzer M, Hudelmaier M, Jackson RD, Yu J, *et al*. Two year longitudinal change and test-retest-precision of knee cartilage morphology in a pilot study for the osteoarthritis initiative. Osteoarthritis Cartilage 2007;15:1326–32.
34. Faber SC, Eckstein F, Lukasz S, Muhlbauer R, Hohe J, Englmeier KH, *et al*. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. Skeletal Radiol 2001;30:144–50.
35. Eckstein F, Charles HC, Buck RJ, Kraus VB, Remmers AE, Hudelmaier M, *et al*. Accuracy and precision of quantitative assessment of cartilage morphology by magnetic resonance imaging at 3.0T. Arthritis Rheum 2005;52:3132–6.
36. Hudelmaier M, Wirth W, Wehr B, Kraus VB, Wyman BT, Hellio Le Graverand M-P, *et al*. Femorotibial cartialge morphology – reproducibility, of different metrics and femoral regions, and sensitivity to change in disease. Cells Tissues Organs 2010.
37. Eckstein F, Buck RJ, Burstein D, Charles HC, Crim J, Hudelmaier M, *et al*. Precision of 3.0 Tesla quantitative magnetic resonance imaging of cartilage morphology in a multicentre clinical trial. Ann Rheum Dis 2008;67:1683–8.
38. Hellio Le Graverand MP, Buck RJ, Wyman BT, Vignon E, Mazzuca SA, Brandt KD, *et al*. Subregional femorotibial cartilage morphology in women – comparison between healthy controls and participants with different grades of radiographic knee osteoarthritis. Osteoarthritis Cartilage 2009;17:1177–85.
39. Buck RJ, Wyman BT, Le Graverand MP. Osteoarthritis may not be a one-way-road of cartilage loss–comparison of spatial patterns of cartilage change between osteoarthritic and healthy knees. Osteoarthritis Cartilage 2010;18(3):329–35.